REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 1-30 and 32 are requested to be cancelled. The cancellation of claims does not constitute acquiescence in the propriety of any rejection set forth by the Examiner. Applicants reserve the right to pursue the subject matter of the canceled claims in subsequent divisional applications.

Claim 31 is currently being amended to recite an hPTH(1-84) preparation "free of human derived proteins and human infectious agents" and which does not contain chemically modified amino acids."

Exemplary support for the claim amendments is found throughout the specification. For example, support for the phrase "free of human derived proteins and human infectious agents" flows from Applicants' disclosure teaching that the described hPTH is not is not isolated from human sources. Additionally, support for the phrase "does not contain chemically modified amino acids" flows from Applicants' disclosure teaching that described hPTH is not made synthetically. See U.S. Patent No. 5,010,010 at col. 1, lines 20-27, which corresponds to Applicants' 1986 priority document.

Upon entry of this Amendment, claims 31 and 33-42 will remain pending in the application. Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. September 27, 2004 Interview

Applicants thank the Examiner for the interview on September 27, 2004. The foregoing amendments and the following remarks incorporate suggestions made by the Examiner during the interview. Specifically, Applicants have deleted claim language referring to a percent purity of the claimed hPTH. Rather, the claimed hPTH, as amended, is distinguished from the prior art on the basis of components present in the composition.

For example, as described in more detail below, PTH isolated from human glands is distinguishable from the claimed hPTH as such isolated hPTH contains contaminating human proteins and/or infectious agents. In addition, synthetic PTH is distinguishable from the claimed hPTH as such synthetic PTH contains chemically modified protecting groups. Both contaminating human proteins and/or infectious agents and chemically modified protecting groups are undesirable, as such materials affect the biological activity of PTH and may cause the PTH preparation to be sufficiently different from the endogenously produced peptide to produce unwanted immunological responses in a patient receiving the hormone as a drug to treat disease.

III. Response to Issues Raised by Examiner in Outstanding Office Action

A. Request for Information Under 37 C.F.R. § 1.105

The Examiner requires Applicants to provide all pertinent information regarding the source of the protein used as a standard. The Examiner notes that the specification at page 7 teaches the use of an hPTH (1-84) standard.

1. July 27, 2004 Declaration of Dr. Kaare Gauvik

Applicants attach as Exhibit 1 a Declaration of Dr. Kaare Gautvik pursuant to 37 C.F.R. § 1.132 dated August 27, 2004 (hereafter "Declaration 1"), which relates to the hPTH (1-84) standard referred to at page 7 of the specification. The hPTH (1-84) standard is synthetic hPTH (1-84) obtained from chemical supply companies, including Peptide Institute Protein Research Foundation, Penninsula Laboratories, Sigma, and Bachem.

The Declaration describes an SDS-PAGE gel in which 0.2 μg of hPTH (1-84) was loaded into various lanes. The hPTH (1-84) was obtained from: (a) Peptide Institute Protein Research Foundation (lane 2), Penninsula Laboratories (lane 3), Sigma (lane 4), or Bachem (lanes 5 and 6), or (b) produced according to the claimed invention (lanes 7, 8, and 9).

A picture of the SDS-PAGE gel is provided in Exhibit B of the attached Declaration.[1] The SDS-PAGE gel confirms that the synthetic hPTH (1-84) obtained from Peptide Institute Protein Research Foundation, Penninsula Laboratories, Sigma, and Bachem contains impurities as compared to the hPTH (1-84) produced according to the claimed invention.

While the synthetic hPTH (1-84) obtained from the various chemical companies contained impurities, the synthetic hPTH(1-84) preparations were useful as standards in confirming the identity of hPTH (1-84) produced according to the claimed invention.

2. September 30, 2004 Declaration of Dr. Kaare Gauvik

Applicants also attach as Exhibit 2 a Declaration of Dr. Kaare Gautvik pursuant to 37 C.F.R. § 1.132 dated September 30, 2004 (hereafter "Declaration 2"), which describes how the impurities discussed in Declaration 1 result in decreased PTH activity. Declaration 2 provides exemplary data for two of the synthetic PTH standards detailed in Declaration 1; from Sima and Bachem Fine Materials.

Paragraphs 5-8 of Declaration 2 describe a comparison of the purity of Applicants' hPTH(1-84) and Bachem's synthetic PTH via silver-stained SDS-PAGE analysis. The resulting gel shows that Applicants' recombinant hTPH (1-84) was assessed to be more than 95% pure. In contrast, the Bachem synthetic PTH preparation contained significant small molecular weight impurities, as demonstrated by the blurry bottom edge of the gel band (Exhibit B of Declaration 2).

[1] Exhibit B is a reproduction of a photograph of the SDS-PAGE gel. Applicants showed the Examiner the original photograph of the gel at the September 27, 2004 interview and the Examiner made a photocopy of the gel for her files.

Paragraphs 9-16 of Declaration 2 discuss data showing that the impurities present in Bachem's synthetic PTH resulted in significantly reduced biological activity as compared to Applicants' claimed PTH(1-84). This reduced biological activity clearly indicates the non-authentic nature of the Bachem synthetic PTH preparation.

For example, the ability of the Bachem synthetic PTH preparation to bind to the receptor and induce cAMP production in cultured cells transfected with the rat PTH receptor was reduced by 40%, as compared to recombinant hPTH(1-84) from *E. coli* and yeast. *See* ¶ 10 of Declaration 2. Further, when tested *in vivo*, a similar reduced biological activity was observed for the Bachem synthetic PTH as compared to recombinant hPTH(1-84). This was determined by (a) measuring different PTHs' ability to increase blood calcium and (b) measuring changes in urinary cAMP, following injection of the two different PTH preparations to rats having their parathyroid hormone glands removed. *See* ¶¶ 11-16 of Declaration 2.

Paragraphs 17-19 of Declaration 2 describe the significant impurities present in Sigma's synthetic PTH as compared to Applicants' claimed hPTH(1-84). As discussed in Declaration 2, after two HPLC purifications steps, the recombinant hPTH(1-84) and the Sigma synthetic PTH elute as a peak showing a symmetrical profile. *See* ¶ 18 of Declaration 2. However, an analytical gel electrophoresis with material from the two peaks after the second HPLC, carried out via silver staining of an SDS-PAGE gel, showed that the Sigma synthetic PTH preparation contained a significant high molecular weight impurity, in addition to low weight impurities shown under the PTH band. *See* ¶ 19 of Declaration 2.

Finally, paragraphs 20-22 demonstrate that the impurities present in Sigma's synthetic PTH result in significantly reduced biological activity as compared to Applicants' claimed hPTH (1-84). This was demonstrated in an adenylate cyclase assay of recombinant hPTH(1-84) and the Sigma synthetic PTH. The relevant adenylate cyclase assay activity of the recombinant PTH(1-84) was shown to be significantly greater than that for the Sigma synthetic PTH. See ¶ 21-22 of Declaration 2.

B. Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 31-35 are rejected by the Examiner under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. Applicants respectfully disagree with the Examiner and traverse this ground for rejection.

Applicants have canceled claim 32. Therefore, the rejection of claim 32 is moot.

With respect to claims 31 and 35, for the sole reason of expediting prosecution of the present application, Applicants have deleted the term "substantially homogenous" from the claims and have amended claim 31 to recite "[a] hPTH (1-84) preparation free of human derived proteins and human infectious agents, wherein the PTH preparation does not contain chemically modified amino acids." Exemplary support for the claim amendment and is found throughout the specification. For example, support for the phrase "free of human derived proteins and human infectious agents" flows from Applicants' disclosure teaching that the described hPTH is not is not isolated from human sources. Additionally, support for the phrase "does not contain chemically modified amino acids" flows from Applicants' disclosure teaching that described hPTH is not made synthetically. *See* U.S. Patent No. 5,010,010 at col. 1, lines 20-27, which corresponds to Applicants' 1986 priority document. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

C. Claim Rejections - 35 U.S.C. § 102

1. Rejection of Claims 31-35 Over Brewer

Claims 31-35 are rejected by the Examiner under 35 U.S.C. § 102(b) as being allegedly anticipated by Brewer et al. (U.S. Patent No. 3,886,132) ("Brewer"). Applicants respectfully request reconsideration and withdrawal of the rejection.

a. Claims 31-32

With respect to claims 31 and 32, the Board refers to page 5 of the Examiner's Answer where the Examiner reasoned that Brewer's "preparation was pure enough to sequence 34 amino acid residues starting at the amino terminus of the protein. Thus, the protein as purified by Brewer et al. appears to be consistent with the limitations in the instant claims with respect to being 'substantially homogenous' hPTH." In

response, the Board states that it is unclear from the specification what degree of purity is intended by "substantially homogenous."

Applicants have canceled claim 32. Therefore, the rejection of claim 32 is moot.

With respect to claim 31, Applicants have amended claim 31 to recite "[a] hPTH (1-84) preparation free of human derived proteins and human infectious agents..." In contrast, Brewer purified hPTH from dried, defatted parathyroid tissue. Therefore, the claimed hPTH is distinct from Brewer's hPTH. Furthermore, this distinction is consistent with the Board's analysis of Brewer.

As described below, the presence of human derived proteins is undesirable because contaminating proteins of human origin are known to induce serious immunological reactions which may develop into autoimmune diseases. The presence of human infectious agents is undesirable because of the serious risk of infection and disease.

i. Contaminating Proteins of Human Origins Cause Undesirable Effects

A drawback to contaminating proteins of human origin is that they are known to induce serious immunological reactions which may develop into autoimmune diseases.

Examples of human proteins known from the literature that can cause autoimmune diseases are mitochondrial proteins and cell surface proteins, both of which would be present in a PTH preparation isolated from pituitary glands, such as the preparation described by Brewer. *See e.g.*, Thakker, *Cell Calcium,* 35(3):275-82 (2004) (Exhibit 3) (describing how auto-antibodies to the cell surface protein CaSR, expressed in the parathyroid, have been found in patients with autoimmune hypoparathyroidism); Li et al., *J. Clin. Invest., 97*(4):910-4 (1996) (Exhibit 4) (describing how the cell surface protein CaSR has been identified as an autoantigen in autoimmune polyglandular syndrome and autoimmune hypothyroidism, both of which are examples of acquired hypoparathyroidism); Weetman, *Thyroid, 4*(4):493-9 (1994)

(Exhibit 5) (describing how antigens expressed by thyroid follicular cells may be exacerbate autoimmune injury, as well as the pathogenesis of autoimmune hypothyroidism). Examples of conditions caused by antibodies against such proteins are development of thyroid autoimmune disease due to generation of anti mitochondrial antibodies, and anti-thyroid stimulating hormone receptor (TSH) antibodies. *See* Lazarus et al., Proc. R. Coll. Physicians Edinb, 31:180-185 (2001) (Exhibit 6).

Moreover, human PTH glands share surface ligands with other human cells. Such other human cells would therefore be targets for autoimmune antibodies produced following human administration of PTH gland constituents, such as those taught by Brewer, with the intent of treating a condition amenable to PTH administration.

ii. Contaminating Infectious Agents From Viral, Prion, or Unknown Sources Cause Undesirable Effects

Examples of undesirable infectious agents potentially present in human biological fluids include, for example, human viral infectious agents, human prion infectious agents, and human bacterial infectious agents.

As PTH is present in humans in very small quantities, to purify human PTH from human sources, collection of glands from many humans is required. This has been achieved by organizing a grand international collection of surgical specimens from both the US and Europe, totaling 0.5 kilogram of human gland material. *See* page 1647 of Keutmann et al., *Biochemistry*, 13(8):1646-1652 (1974) (Exhibit 7); and page 384 of Niall et al., *Proc. Natl. Acad. Sci, USA*, 71(2):384-388 (1974) (Exhibit 8). Using this large quantity of starting material, researchers attempted to isolate native human PTH.

However, because such a large number of sources were required to obtain the necessary quantity of gland material that would enable isolation of naturally occurring PTH, the likelihood that the resultant isolated PTH would contain undesirable infectious materials is great. This is because the presence of such infectious materials in a single human gland would provide a common source for spreading infection; an infection by only one source would contaminate the whole preparation.

An example of contamination occurring following isolation of a hormone from a large pool of donors is isolation of human growth hormone (HGH) prepared from many collected pituitary glands taken post-mortem. After purification of the hormone, it was used to treat pituitary dwarfism in children in the 1970s and 1980s. The hormone was injected, as would be required for PTH administration, and several cases of Creutzfeldt-Jakob disease (CJD) occurred. CJD is a rare and incurable virus infection that attacks the brain and central nervous system. While CJD is extraordinarily rare, three patients treated with naturally derived HGH were diagnosed with CJD. Due to fears that the hormone preparation was contaminated with the rare virus, the U.S. Food and Drug Administration (FDA) closed off the U.S. market of naturally derived HGH in April 1985. Soon afterward, officials in Britain, the Netherlands, Belgium, Sweden, and Greece followed the FDA's lead and banned the use of naturally derived HGH. *See* "U.S. halts Distribution of Growth Hormone as Precaution After 3 Deaths," *The New York Times*, April 20, 1985 (Late City Final Edition), Section 1; Page 7, Column 1, National Desk (Exhibit 9) and "The Race for Synthetic Human Growth Hormone," *Chemical Week*, July 10, 1985, Specialties Section, page 28 (Exhibit 10).

Another example is the spread of hepatitis virus and other neurotropic viruses, such as human immunodeficiency virus, carried by preparations containing serological or tissue constituents from humans. *See,* page 3 of Horowitz, L.G., "Emerging Viruses: AIDS & Ebola: Nature, Accident or Intentional" http://www.whale.to/vaccines/martin1.html (Exhibit 11) and page 2 of Cantwell, A. "Are Vaccines Causing More Disease Than They are Curing?" http://www.med-help.net/PageAAA.htm (Exhibit 12).

b. Claims 33-35

With respect to claims 33-35, the Examiner asserts that the product-by-process limitations are drawn to recombinant production of the claimed "substantially homogenous hPTH (1-84)", which as been found anticipated by Brewer, as affirmed by the BPAI. As discussed above, the product of claim 31 is not anticipated by Brewer. Therefore, claims 33-35 are also not anticipated by Brewer.

2. Rejection of Claims 31-35 as being Allegedly Anticipated by Applicants' "standard" hPTH (1-84)

The Examiner asserts that the specification at page 7 teaches the use of an hPTH (1-84) standard to compare and assess the results of the purification process. Further, the Examiner asserts that for the "standard" to have been useful for such comparison, it itself must have met the limitations of the pending claims.

Applicants respectfully disagree with the Examiner. However, to expedite prosecution, Applicants have amended claim 31 to recite "wherein the PTH preparation does not contain chemically modified amino acids." As discussed above, the PTH standard, referred to on page 7 of the specification, is synthetic PTH obtained from chemical supply companies, including Peptide Institute Protein Research Foundation, Penninsula Laboratories, Sigma, and Bachem. All of the synthetic PTH preparations necessarily contain chemically modified amino acids, such as protecting groups, resulting from the chemical processes used to make the compounds.

Moreover, as described in Declaration 1, SDS-PAGE analysis of the five different synthetic PTH standards as compared to recombinant hPTH (1-84) of the claimed invention, showed that all of the five synthetic PTH compositions used as standards contained impurities. Further, as described in Declaration 2, such impurities result in decreased biological activity of the synthetic PTH and may elicit potential autoimmune reactions.

Because the synthetic PTH used by Applicants' as a PTH standard is explicitly excluded from the claimed invention, and because such PTH standards have lower biological activity as compared to Applicants' claimed hPTH(1-84), withdrawal of this ground for rejection is respectfully requested.

3. New Claims 36-42 are not Anticipated by Brewer

New claims 36-42 are not anticipated by Brewer because these claims are directed to hPTH(1-84) comprising a sequence containing at least one amino acid selected from the group consisting of a glutamate at position 22, a leucine at position

28, and an aspartate at position 30. This hPTH(1-84) sequence is not taught or suggested by Brewer.

As shown in Figure 1 of Brewer, the amino acids at positions 22, 28, and 30 are glutamine, lysine and leucine, respectively. In contrast, the amino acids at positions 22, 28, and 30 in the hPTH(1-84) of claims 36-42 are glutamate, leucine, and/or aspartate, respectively (see sequence alignment provided below). Therefore, claims 36-42 are not anticipated by Brewer.

```
Brewer:     1  SVSEIQLMHNLGKHLNSMERVQWLRKKKQLVHNF 34
               SVSEIQLMHNLGKHLNSMERV+WLRKK Q VHNF
Invention:  1  SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF 34
```

D. Claim Rejections - 35 U.S.C. § 103

1. Rejection of Claims 31-35 Over Breyel or Mayer et al., in view of Kaisha et al. and Brewer et al.

Claims 31-35 are rejected by the Examiner under 35 U.S.C. § 103 as being allegedly obvious over Breyel et al., "Synthesis of mature human parathyroid hormone in Escherichia coli," *Third European Congress on Biotechnology*, Vol. 3, p. 363-369 (1984) ("Breyel"), or Mayer et al., EP 0 139 076 ("Mayer"), in view of Kaisha et al., GB 2 092 596 ("Kaisha"), and Brewer et al., U.S. Patent No. 3,886,132 ("Brewer")

The Examiner asserts that although Breyel fails to disclose a hPTH that was purified from bacterial cell extracts, and Mayer fails to teach purification to the degree recited in the rejected claims, a person of ordinary skill in the art would have been motivated to purify the hPTH as taught by Breyel or Mayer using the protocol suggested by Brewer because Kaisha teaches the desirability of making large quantities of hPTH.

Applicants have canceled claim 32. Therefore, the rejection of claim 32 is moot. With respect to claims 31 and 33-35, Applicants respectfully request reconsideration and withdrawal of the rejection.

a. The Rejection is Flawed Because the Purification Method of Breyel or Mayer Could not be Used to Purify Brewer's Biological Material

A proper rejection for obviousness under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition, or device, or carry out the claimed process and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art, and not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438 (Fed. Cir. 1991).

The cited combination of references does not obviate the claimed invention because a person of ordinary skill in the art would know that the purification procedure used to purify the hPTH of Breyel or Mayer *could not* be the same purification procedure used to purify the hPTH of Brewer. This is because the hPTH of Breyel and Mayer were derived from entirely different sources than the hPTH of Brewer.

Specifically, the hPTH of Brewer was purified from dried, defatted parathyroid tissue. In contrast, Breyel and Mayer disclosed expression of hPTH in *E. coli* (*see* page 363, "Summary," of Breyel and page 12, line 7 of Mayer). *E. coli* has endogenous exopeptidase and endopeptidase activity which cleaves internal protease sensitive domains in PTH. *See* Mathavan et al., "High Level Production of Human Parathyroid Hormone in *Bombyx mori* Larvae and BmN Cells Using Recombinant Baculovirus," *Gene, 167:*33-39, at 34 (1995) (Exhibit 13). Therefore, the hPTH of Breyel and Mayer contained *fragments* of hPTH. *See e.g.,* page 2, line 34, through page 3, line 8, of the specification, where it is noted that Breyel demonstrated *E. coli* degradation of human PTH.

The cited art would not have suggested to those of ordinary skill in the art that they should, or could, purify the hPTH of Breyel or Mayer utilizing the purification procedure disclosed in Brewer. This is because a person of ordinary skill in the art would know that the hPTH of Breyel and Mayer contained significant amounts of hPTH fragments, since the hPTH material was expressed in *E. coli*. In contrast, the hPTH of

Brewer did not contain hPTH fragments, since it was obtained from dried, defatted parathyroid tissue.

b. One of Skill in the Art Would not Have a Reasonable Expectation of Success in Applying the Purification Process of Brewer to the hPTH Fragments of Breyel or Mayer

Furthermore, a person of ordinary skill in the art would not have had a reasonable expectation of success in applying the hPTH purification procedure of Brewer to the hPTH fragments of Breyel and Mayer to obtain hPTH(1-84) that meets Applicants' claim limitations. This is because purifying hPTH(1-84) from hPTH fragments would be extremely difficult because the chromatographic properties of hPTH fragments would be similar to the chromatographic properties of intact hPTH(1-84). Thus, the generic three step purification procedure described in Brewer, when applied to the hPTH of Breyel and Mayer, would not result in intact hPTH (1-84) meeting the limitations of Applicants' claims.

At best, the Examiner is using an improper "obvious to try" standard, arguing that it would have been obvious to a person of ordinary skill in the art to *try* to purify the hPTH of Breyel or Mayer utilizing the purification procedure disclosed in Brewer. However, "'obvious to try' has long been held to not constitute obviousness." *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995).

Applicants also note that the hPTH of Breyel is not "mature" PTH, as "mature" PTH consists only of the known and correct 84 amino acids of PTH, and does not additionally include other fused amino acid residues. *See e.g.,* Mahoney, WO 84/01173, at page 12, lines 1-2 and 33-37; and page 13, lines 27-32, referring to a "mature" protein (Exhibit 14). Nor does "mature" PTH include chemical modifications well known to occur to most peptides synthesized in *E. coli*. *See e.g.,* Høgset et al., "Expression of Human Parathyroid Hormone in *E. coli*" *BBRC*, Vol. 166, p. 50-60 (1990) (Exhibit 15); Kareem, B. et al., "Translocation and Processing of Various Human Parathyroid Hormone Peptides in *E. coli* and Differentially Effected by Protein-A-Signal Sequence Mutations" *European Journal of Biochemistry*, Vol. 22, p. 893-900 (1994) (Exhibit 16); and Kareem et al., A Method for the Evaluation of the Efficiency of Signal Sequences for Secretion and Correct N-terminal Processing of Human Parathyroid

Hormone Produced in *E. coli*" *Analytical Biochemistry*, Vol. 204, p. 26-33 (1992) (Exhibit 17).

c. The Teachings of the Cited Art Fail to Disclose Each and Every Limitation of the Claimed Invention.

As discussed above, the PTH of Brewer does not meet Applicants' claim limitations. None of Breyel, Mayer, or Kaisha cure the deficiencies of Brewer. Therefore, claims 31-35 are not obvious over the combined teachings of Breyel, Mayer, Kaisha, and Brewer.

2. New Claims 36-42 are not obvious over Breyel or Mayer, in view of Kaisha and Brewer

New claims 36-42 are not obvious over Breyel or Mayer, in view of Kaisha and Brewer for the reasons discussed above.

III. CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant(s) hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

10/7/04
Date

#46785
Michele M. Simkin
Attorney for Applicant
Registration 34,717

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5538
Facsimile: (202) 672-5399